nature cell biology

Review article

https://doi.org/10.1038/s41556-024-01360-8

A guideline on the molecular ecosystem regulating ferroptosis

Received: 1 September 2023

Accepted: 18 January 2024

Published online: 29 February 2024

Check for updates

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Ferroptosis, an intricately regulated form of cell death characterized by uncontrolled lipid peroxidation, has garnered substantial interest since this term was first coined in 2012. Recent years have witnessed remarkable progress in elucidating the detailed molecular mechanisms that govern ferroptosis induction and defence, with particular emphasis on the roles of heterogeneity and plasticity. In this Review, we discuss the molecular ecosystem of ferroptosis, with implications that may inform and enable safe and effective therapeutic strategies across a broad spectrum of diseases.

Ferroptosis, coined in 2012, is a form of iron-dependent regulated cell death distinct from apoptosis[1]. Unlike lytic cell death executed by pore-forming proteins, ferroptosis is driven by toxic oxidized lipids and their byproducts, notably 4-hydroxynonenal (4HNE)[2], along with lipidated proteins formed through covalent binding to breakdown products of electrophilic lipid peroxidation[3].

Ferroptosis has multiple implications in preclinical studies across a range of diseases, including cancer, neurodegenerative disorders and conditions associated with ischaemia–reperfusion (I/R) injury. It offers a promising therapeutic approach against drug-resistant cancer cells deficient in apoptosis[4,5], whereas its inhibition holds the potential for managing infection-related diseases, sterile inflammation linked to iron overload or lipid toxicity[6,7]. In addition, ferroptosis plays a vital role in tissue homeostasis and development[8–10].

In this Review our aim is to offer an updated overview of ferroptosis, covering its fundamental mechanisms, heterogeneity and plasticity. We will also delve into the integrated antioxidant and membrane system's role in regulating ferroptotic sensitivity, and discuss disease implications, therapeutic prospects and associated challenges.

The core mechanism of ferroptosis

Erastin and RSL3 are common small molecules used to induce ferroptosis. Originally discovered in screens targeting *RAS*-mutant cancer cells, these compounds trigger a non-apoptotic iron-dependent form of cell death, leading to the term 'ferroptosis'[1,11,12]. At the same time, genetic inactivation of glutathione peroxidase 4 (GPX4) was found to induce oxidative non-apoptotic cell death[13] and overexpression of system x_c^- (also known as xCT) to protect cells from a similar non-apoptotic cell death[14], highlighting the generality of this process as a potential cancer therapy targeting *RAS* mutations while sparing normal cells.

Further research has revealed that ferroptosis is highly context-dependent. Metal ions such as zinc and copper (in addition to iron) can

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https://doi.org/10.1038/s41556-024-01360-8

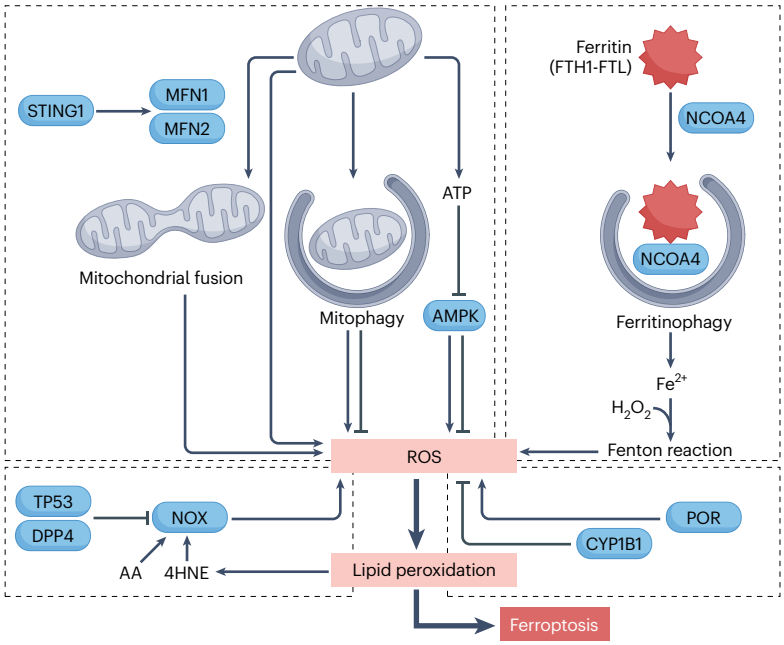

Fig. 1 | Production of ROS in ferroptosis. The initiation of ferroptosis requires an oxidative environment, facilitated by diverse sources of ROS. Mitochondrial ROS, generated mainly through the electron transport chain, can trigger ferroptosis in specific conditions. Mitophagy, involved in removing damaged mitochondria, has a dual role in promoting or inhibiting ferroptosis, whereas mitochondrial fusion increases cellular sensitivity to ferroptosis. Activation of the mitochondrial stimulator of interferon response cGAMP interactor 1 (STING1) promotes mitochondrial fusion, leading to ROS production implicated in ferroptosis. Mitochondrial energy stress activates AMPK, which can promote or inhibit ferroptosis by phosphorylating different substrates. NOX enzymes in cell membranes play a crucial role in generating ROS in ferroptosis. TP53 inhibits NOX-mediated ferroptosis by binding to DPP4, whereas arachidonic acid (AA) and 4HNE enhance NOX1 activity to promote ROS production. POR promotes ROS production and ferroptosis, whereas cytochrome P450 family 1 subfamily B member 1 (CYP1B1) inhibits ferroptosis. Ferritinophagy involves the degradation of the iron storage protein ferritin, releasing Fe^{2+} that triggers ROS production through the Fenton reaction.

induce ferroptosis in specific conditions[15,16]. Both *RAS*-wild-type cells and *RAS*-mutant cells, including cancer and non-cancer cells, can undergo ferroptotic death. Conditional knockout of *Gpx4* in various tissues (for example, kidney[8]) or cells (for example, T cells[10] or B cells[9]) can cause ferroptotic damage, highlighting its role in developmental biology.

Ferroptosis is closely linked to autophagy, and heightened autophagy levels often correlate with increased ferroptosis sensitivity[17]. Specific types of selective autophagy (such as ferritinophagy[18,19], lipophagy[20] and clockophagy[21]) lead to iron accumulation and lipid peroxidation, inducing ferroptosis. Genome-wide CRISPR interference and activation screens in human neurons revealed that autophagy-related (ATG) family members (for example, beclin 1 (BECN1)) and lysosomal proteins (for example, prosaposin (PSAP)) are involved in ferroptosis by triggering the formation of lipofuscin or increasing iron accumulation[22]. In certain conditions, including ferroptosis, the depletion of *ATG* genes has no effect on cell death.

These findings underscore the adaptable and context-dependent nature of ferroptosis, but its initiation involves three essential elements—reactive oxygen species (ROS), oxidizable lipids and lipid peroxidation—which will be discussed next.

ROS

The first crucial element in ferroptosis induction is the presence of initiation signals that stimulate the production of ROS from various sources (Fig. 1):

1. Mitochondria. Mitochondria serve as a major source of ROS, mainly superoxide anion ($O_2^{\bullet-}$) during oxidative phosphorylation. Mitochondrial superoxide dismutase (SOD) converts superoxide into other ROS, including hydrogen peroxide. Mitochondrial ROS can trigger ferroptosis, with glutaminolysis promoting ferroptosis induced by cyst(e)ine deprivation[23,24]. Mitochondrial quality is regulated by mitophagy, which has a dual role in ferroptosis. Whereas mitochondrial fission promotes apoptosis[25], mitochondrial fusion can increase cellular sensitivity to ferroptosis[26]. Mitochondrial energy stress inhibits ferroptosis through the AMP-activated protein kinase (AMPK)-mediated phosphorylation of acetyl-CoA carboxylase α (ACACA; also known as ACC)[27], but activated AMPK can also promote ferroptosis by targeting BECN1 (ref. 28) or by regulating pyrimidinosome assembly[29].
2. NADPH oxidase (NOX). Overexpression of NOX increases ROS levels, heightening ferroptosis sensitivity. The activity of NOX in ferroptosis is regulated by multiple factors, such as tumour protein p53 (TP53)[30] and aldehyde dehydrogenase 1 family member B1 (ALDH1B1)[2]. TP53 deficiency promotes the accumulation of dipeptidyl peptidase 4 (DPP4) on the cell membrane, forming a complex with NOX1 and causing ferroptotic death[30]. ALDH1B1 inhibits the ferroptosis-inducing effect of NOX1 activity by catalysing the oxidation of aldehydes, converting them into carboxylic acids[2].
3. Enzymatic reactions. ROS can be byproducts of enzymatic reactions such as cytochrome P450 and its reductase involved in drug metabolism. Cytochrome P450 oxidoreductase (POR), a flavoprotein, induces lipid peroxidation and ferroptosis by generating superoxide radicals[31,32].
4. The Fenton reaction. This reaction involves the interaction between hydrogen peroxide and a transition metal, typically iron (Fe^{2+}), leading to the generation of highly reactive hydroxyl radicals ($HO^{\bullet}$). An extensively studied iron metabolism mechanism during ferroptosis is ferritinophagy, in which autophagy degrades the iron storage protein ferritin. This liberates free iron, converting one ROS type into another, thereby inducing ferroptosis in both cancer and non-cancer cells[18,19].

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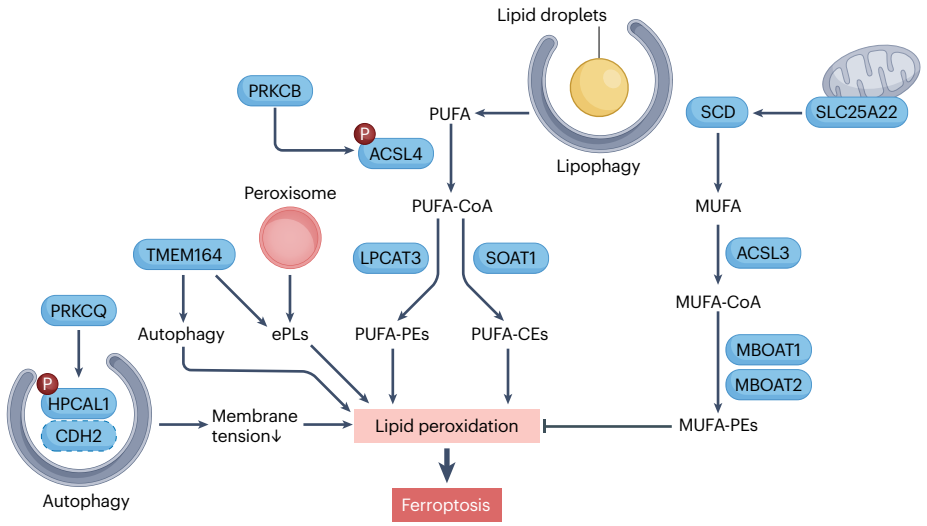

Fig. 2 | Lipid resources for ferroptosis. Cell membranes are the primary target of oxidative damage in ferroptosis, influenced by processes and metabolic pathways that promote lipid synthesis. ACSL4 plays a critical role in activating PUFAs by converting them into acyl-CoA esters (PUFA-CoA), which serve as substrates for lipid peroxidation, contributing to the initiation of ferroptosis. Two downstream pathways involve LPCAT3-mediated PUFA-PEs and sterol *O*-acyltransferase 1 (SOAT1)-mediated PUFA-CEs. The activity of ACSL4 in ferroptosis is further enhanced by PRKCB-mediated ACSL4 phosphorylation. Hippocalcin-like 1 (HPCAL1) phosphorylation (P) by PRKCQ promotes ferroptosis by inducing autophagic degradation of cadherin 2 (CDH2), leading to alterations in membrane tension in cancer cells. Stearoyl-CoA desaturase (SCD) and ACSL3-mediated MUFA synthesis counteracts the initiation of ferroptosis by protecting against PUFA peroxidation. The mitochondrial transporter solute carrier family 25 member 22 (SLC25A22) inhibits ferroptosis by facilitating the production of SCD-mediated MUFA. MBOAT1 and MBOAT2 inhibit ferroptosis by remodelling the cellular phospholipid profile to produce MUFA-PEs. Peroxisomes contribute to the biosynthesis of ether phospholipids (ePLs), which are vulnerable to lipid peroxidation. TMEM164 functions as an acyltransferase involved in ePL synthesis or promotes the formation of phagophores and autophagosomes to facilitate autophagy. Lipophagy, the degradation of lipid droplets by autophagy, releases lipids that can undergo peroxidation, increasing the susceptibility of cells to ferroptosis. In contrast, the heightened accumulation of lipid droplets hinders ferroptosis.

Oxidizable lipids

The second key element in ferroptosis is the presence of easily oxidizable polyunsaturated lipids (Fig. 2). Cell membranes, the primary target of oxidative damage in ferroptosis, can be influenced by metabolic pathways that promote lipid synthesis, particularly the generation of polyunsaturated fatty acids (PUFAs), increasing cell sensitivity to ferroptotic inducers. Although the exact threshold for PUFA breakdown required to initiate ferroptosis remains obscure, one well-established positive regulator is acyl-CoA synthetase long-chain family member 4 (ACSL4). ACSL4 activates long-chain fatty acids by converting them into acyl-CoA esters, facilitating their entry into various metabolic pathways[33–36].

ACSL4 mediates at least two downstream pathways, yielding different PUFA-related acyl-CoA esters. One involves lysophosphatidylcholine acyltransferase 3 (LPCAT3) incorporating PUFA into phosphatidylethanolamines (PEs)[33,34,36], whereas the other activates sterol *O*-acyltransferase 1-producing PUFA-cholesteryl esters (CEs) instead of PUFA-PEs[37]. Both pathways contribute to lipid peroxidation, acting as substrates depending on the context. In human pancreatic cancer cells deficient of the lipid flippase solute carrier family (SLC) 47 member 1 (*SLC47A1*), ACSL4-driven PUFA-CE production is particularly relevant[37]. ACSL4 activation is a strategy for enhancing the efficacy of chemotherapy or immunotherapy by inducing ferroptosis in solid cancers[38]. Protein kinase C-β (PRKCB; also known as PKCβII) enhances ACSL4 activity via Thr328 phosphorylation[39], whereas phosphorylation of hippocalcin-like 1 at Thr149 by protein kinase C-θ (PRKCθ; also known as PRKCQ) induces ferroptosis by autophagic degradation of cadherin 2 (CDH2), altering membrane tension in cancer cells[40].

ACSL3 synthesizes monounsaturated fatty acids (MUFAs), which may competitively inhibit PUFA peroxidation, providing protection against ferroptosis initiation[41,42]. The mitochondrial glutamate transporter SLC25A22 inhibits ferroptosis in pancreatic cancer cells by enhancing glutathione (GSH) and MUFA synthesis[43]. Membrane-bound *O*-acyltransferase domain-containing 1 (MBOAT1) and MBOAT2, which are upregulated by sex hormone receptors, inhibit ferroptosis in cancer cells by remodelling the cellular phospholipid profile to produce MUFA-containing phospholipids[44]. ACSL4-independent pathways add to the complexity of our understanding of lipid metabolism in cell-death regulation[45].

Peroxisomes (involved in fatty acid breakdown, hydrogen peroxide production and PUFA plasmalogen biosynthesis) can increase ferroptosis sensitivity[46]. They also contain antioxidant enzymes such as catalase (CAT), which can inhibit ferroptosis, as well as MUFA plasmalogens, which prevent ferroptosis[47]. Thus, peroxisomes and plasmalogens influence ferroptosis positively or negatively depending on the context.

Lipophagy selectively degrades lipid droplets, releasing lipids for peroxidation, making cells (especially hepatocellular carcinoma cells) more susceptible to ferroptosis[20]. Increased lipid storage in lipid droplets by ACSL3 limits ferroptosis in clear cell renal cell carcinoma cells[48].

Furthermore, transmembrane protein 164 (TMEM164) acts as a positive regulator of ferroptosis by functioning as an acyltransferase, synthesizing C20:4 ether phospholipids[49] and promoting the formation of membrane-driven phagophores[50]. These phagophores are essential for the subsequent creation of autophagosomes in pancreatic cancer cells in response to ferroptotic stimuli, rather than nutrient starvation[50].

Lipid peroxidation

Several enzymes, including arachidonate lipoxygenases (ALOXs), cyclooxygenase (also known as prostaglandin-endoperoxide synthase (PTGS)) and cytochrome P450 enzymes, play a context-dependent role in catalysing lipid peroxidation during ferroptosis (Fig. 3).

ALOXs are enzymes that catalyse PUFA oxygenation, thereby initiating lipid peroxidation through the introduction of hydroperoxy groups (-OOH) into fatty acid chains. Humans have six ALOX isoforms (ALOX5, ALOX12, ALOX12B, ALOX15, ALOX15B and ALOXE3), with

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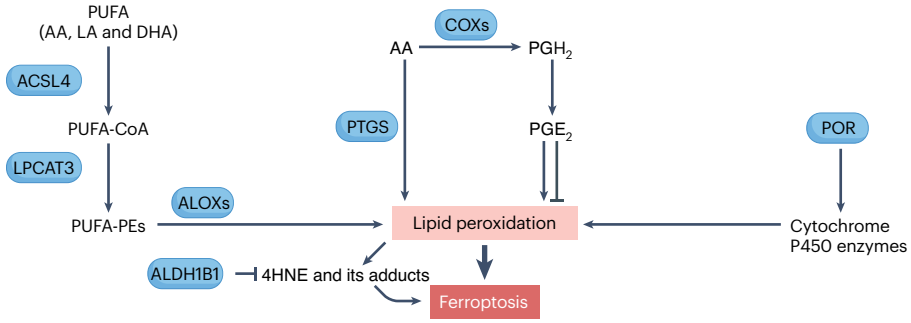

Fig. 3 | Lipid peroxidation in ferroptosis. Several key enzymes—including ALOX, PTGS and cytochrome P450 enzymes—participate in lipid peroxidation. ALOXs are a family of enzymes that catalyse the oxygenation of PUFAs such as arachidonic acid (AA), linoleic acid (LA) and docosahexaenoic acid (DHA), leading to the formation of lipid hydroperoxides. PTGS enzymes are involved in prostaglandin synthesis but can also catalyse lipid peroxidation. The production of prostaglandin H_2 (PGH_2) and subsequently PGE_2 promotes or inhibits ferroptosis in a context-dependent manner. In addition, POR plays a role by supplying electrons to the cytochrome P450 enzymes involved in the production of lipid hydroperoxides. These hydroperoxides can undergo further reactions, such as decomposition and rearrangement, generating highly reactive lipid radicals. Ultimately, this cascade of reactions can disrupt membrane integrity and contribute to ferroptotic cell death. ALDH1B1 metabolizes a wide range of aldehyde substrates, including acetaldehyde, and products of lipid peroxidation (for example, 4HNE).

distinct substrate preferences and catalytic activities, that contribute to ferroptosis in various cells or tissues[42,45,51,52]. PE-binding protein 1 (PEBP1) forms catalytic complexes with ALOX15, efficiently peroxidizing PUFA-PE[53]. Inhibitors that target ALOX15–PEBP1 complexes prevent phospholipid peroxidation and mitigate injuries from total body irradiation in vivo[54]. However, the deletion of *Alox15* does not prevent *Gpx4*-deletion-driven ferroptosis during acute renal failure[8]. Therefore, profiling of ALOX expression in experimental models is crucial to assess the requirement of different ALOX members in ferroptosis.

PTGS enzymes catalyse lipid peroxidation by oxygenating free PUFAs, generating lipid hydroperoxides. However, their primary function is prostaglandin synthesis, playing a secondary role in lipid peroxidation. Prostaglandin E_2 (PGE_2) production inhibits ferroptosis through prostaglandin E receptor 1 (PTGER1) and PTGER2 in cerebral I/R[55] but promotes ferroptosis in acute kidney injury[56].

Cytochrome P450 enzymes (involved in drug metabolism) can catalyse lipid peroxidation by introducing oxygen into fatty acid chains, generating lipid hydroperoxides and 4HNE, which are known ferroptosis mediators. As discussed earlier, POR plays a role by supplying electrons to molecular oxygen, thereby facilitating hydrogen peroxide production for ferroptosis induction[31,32].

Regardless of the enzyme catalysing lipid peroxidation, lipid hydroperoxides initiate a chain reaction. They undergo cleavage reactions, often catalysed by transition metals such as iron, generating highly reactive lipid radicals. These radicals react with nearby lipids, amplifying lipid peroxidation in a self-propagating process[57]. Electrophilic, oxidatively truncated phospholipid variants then form, reacting with amino acid residues in proteins to induce protein lipoxidation[3]. This series of reactions damages cell membranes, altering membrane tension, compromising membrane repair and ultimately leading to ferroptotic plasma membrane permeabilization[58–60]. The endoplasmic reticulum is proposed as the initial site that could result in subsequent oxidative membrane damage in other organelles[61].

Antioxidant systems in ferroptosis

Enzymatic antioxidants

The key enzyme involved in the antioxidant defence against ferroptosis is GPX4, which reduces lipid hydroperoxides to alcohols in biological membranes[62] (Fig. 4). The active centre of GPX4 contains selenocysteine[63,64]. Low selenium levels lead to ribosome stalling at the inefficiently decoded selenocysteine UGA codon of GPX4, causing ribosome collisions, premature translation termination and proteasomal clearance of the amino (N)-terminal GPX4 fragment[65]. The molecular chaperone heat shock protein family A (Hsp70) member 5 (HSPA5) directly stabilizes GPX4 protein[66], whereas autophagy[67,68] and the ubiquitin–proteasome system[69] mediate GPX4 protein degradation, thereby increasing ferroptosis sensitivity. Creatine kinase B-mediated phosphorylation of GPX4 at Ser104 inhibits autophagy-mediated GPX4 degradation and subsequent ferroptosis[68].

The R152H mutation in GPX4 can cause Sedaghatian-type spinal metaphyseal dysplasia, a rare and fatal disease in newborns[70]. In vitro studies suggest that this R152H mutation does not affect the catalytic activity of the enzyme in a direct fashion but rather interferes with its allosteric activation by cardiolipin[71]. Further examination is necessary to determine whether excessive cardiolipin peroxidation by dysfunctional mitochondrial GPX4 contributes to development of the disease.

Constitutive knockout of the *Gpx4* gene in mice leads to death at embryonic days 7.5–8.5 (ref. 72). In vivo evidence linking *Gpx4* deficiency to ferroptosis was first observed in mice with conditional knockout of *Gpx4* in the kidney, combined with a vitamin E-deficient diet, leading to kidney damage[8]. This phenotype is reversed by supplementation with vitamin E or the ferroptosis inhibitor liproxstatin-1 (ref. 8). Similarly, ferroptosis of activated T cells in the absence of *Gpx4* in mice is prevented by a vitamin E-enriched diet[10]. Under normal breeding conditions and chow feeding, the conditional knockout of *Gpx4* in several cell types (for example, myeloid, pancreatic epithelial cells or hepatocytes) is not lethal[73–75]. However, the inducible conditional knockout of *Gpx4* in neurons and homozygous conditional deletion of *Gpx4* in gut epithelium under the standard chow diet are lethal[76,77]. Thus, the protection against lipid peroxidation function provided by GPX4 is context dependent during tissue development.

GSH (a tripeptide composed of glutamate, cysteine and glycine) acts as a GPX4 cofactor. Cysteine, a critical precursor for GSH synthesis, can limit GSH production and is derived from methionine metabolism. In addition, and more importantly, cells import extracellular cystine via the cystine–glutamate antiporter system x_c^-, which is composed of SLC7A11 and SLC3A2 subunits. Imported cystine is subsequently reduced to cysteine. Pharmacological agents such as erastin and sulfasalazine can inhibit system x_c^- (refs. 1,78). At high concentrations, sorafenib reportedly inhibits the activity of system x_c^- in an indirect fashion[78] but a recent study indicated that sorafenib only fails to induce ferroptosis in certain cancer cells[79]. GSH is synthesized mainly in the cytosol through enzymatic reactions[80], and system x_c^- is crucial for maintaining GSH levels to prevent ferroptosis before it begins, as GSH synthesis during ferroptosis onset is too slow.

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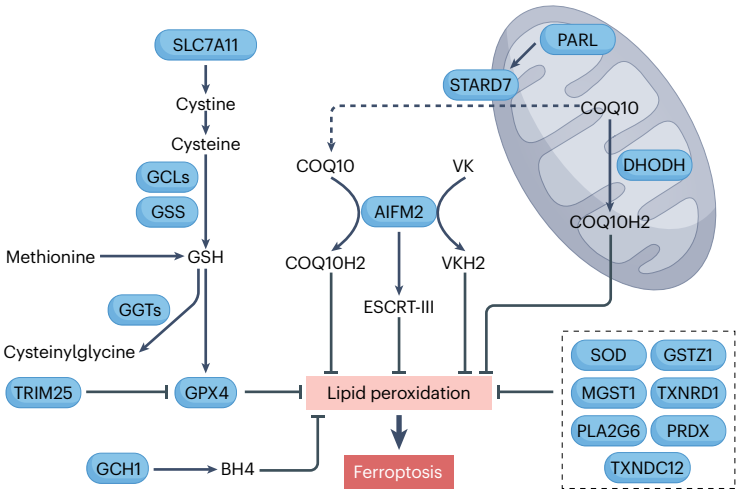

Fig. 4 | Enzymatic antioxidants in ferroptosis. GPX4 is the main enzyme central to the antioxidant defence against ferroptosis; it requires the tripeptide cofactor GSH. SLC7A11 is a key component of the cystine–glutamate antiporter system x_c^- responsible for allowing the uptake of cystine, which is then reduced to cysteine in the cells. TRIM25 mediates GPX4 degradation in a cell type-dependent manner. The synthesis of the majority of cellular GSH involves the rate-limiting substrate cysteine, catalysed by glutamate-cysteine ligases (GCLs, which include a catalytic subunit (GCLC) and a modulatory subunit (GCLM)) and glutathione synthetase (GSS). Cysteine can also be derived from the metabolism of methionine. A family of enzymes called γ-glutamyltransferases (GGT) catalyse the breakdown of GSH into cysteinylglycine and free amino acids. AIFM2 and DHODH play pivotal roles in the reduction of COQ10 to its antioxidant form, COQ10H2, in the plasma membrane/cytoplasm and mitochondria, respectively. The cleavage of STARD7 by PARL is essential for the transport of COQ10 to the plasma membrane/cytoplasm, thereby inhibiting ferroptosis. Furthermore, AIFM2-mediated membrane repair and vitamin K (VK) reduction to its corresponding hydroquinone (VKH2) also contribute to its anti-ferroptotic activity. GCH1 participates in the biosynthesis of BH4, a cofactor that helps maintain cellular redox balance and antioxidant defences, thereby inhibiting susceptibility to ferroptotic cell death. Several other enzymes, such as SOD2 family, MGST1, GSTZ1, TXNRD1, TXNDC12, PLA2G6 and PRDX inhibit ferroptosis in some cases.

Whereas GSH depletion contributes to ferroptosis, GPX4 is not the exclusive target of GSH, suggesting the existence of GPX4-independent protective pathways against ferroptosis (Fig. 4). Among them, apoptosis-inducing factor mitochondria associated 2 (AIFM2; also known as FSP1) relocates from mitochondria to the cell membrane in *Gpx4*-deficient cells, reducing coenzyme Q10 (COQ10) and inhibiting ferroptosis[81,82]. StAR-related lipid transfer domain-containing 7 (STAR7), which is found in both mitochondrial intermembrane space and cytosol after cleavage by the presenilin-associated rhomboid-like (PARL) protein, participates in COQ10 transport to the plasma membrane, also hindering ferroptosis[83]. In addition, AIFM2 contributes to membrane repair[84] and the canonical vitamin K cycle[85,86], enhancing its anti-ferroptotic effects. The activity of AIFM2 in ferroptosis relies on phase separation and can be initiated by N-terminal myristoylation, facilitated by compound icFSP1 (ref. 87).

Dihydroorotate dehydrogenase (quinone; DHODH) is a mitochondrial enzyme involved in pyrimidine biosynthesis, which is crucial for DNA and RNA formation. The activity of DHODH has an influence on the ferroptotic susceptibility of cancer cells expressing low levels of GPX4, probably due the DHODH-catalysed utilization of COQ10 as an electron acceptor[88]. Inhibition of DHODH reduces COQ10, increasing susceptibility to lipid peroxidation and ferroptosis. However, the potential off-target effects of DHODH inhibitors on AIFM2 are debated[89,90].

In addition to GPX4, AIFM2 and DHODH, several other antioxidant enzymes play roles in suppressing ferroptosis. GTP cyclohydrolase 1 (GCH1) is involved in tetrahydrobiopterin (BH4) biosynthesis, contributing to cellular redox balance and ferroptosis inhibition[91]. Mitochondrial SOD2 defends against heat-stress-induced ferroptosis[92]. Nitric oxide synthase 2 (also known as inducible nitric oxide synthase) represses ferroptosis in macrophages by suppressing ALOX15-mediated lipid peroxidation[93]. Nuclear factor erythroid 2-like bZIP transcription factor 2 (NFE2L2; also known as NRF2)-mediated upregulation of microsomal glutathione *S*-transferase 1 (MGST1) aids cellular detoxification in pancreatic cancer cells in response to ferroptotic activators[94]. Glutathione *S*-transferase-ζ1 (GSTZ1) inhibits ferroptosis in bladder cancer cells[95], and thioredoxin reductase 1 (TXNRD1), thioredoxin-domain-containing 12 (TXNDC12) and peroxiredoxins (PRDX) also have context-dependent roles in ferroptosis inhibition[96–99]. In addition, Ca^{2+}-independent phospholipase A2 group VI (PLA2G6; also known as iPLA2β and PNPLA9) plays a role in eliminating ferroptotic death signals by hydrolysing peroxidized membrane phospholipids, potentially mediated by TP53 regulation[100,101]. Understanding the synergistic effects of different antioxidant systems in ferroptosis remains a central theme in translational medicine.

Non-enzymatic antioxidants

Non-enzymatic antioxidants counteract harmful ROS and protect cells from oxidative damage, maintaining cellular redox balance. Examples in ferroptosis include vitamin E, vitamin K, GSH, COQ10 and NADPH[1,81,82,86]. They collaborate with enzymatic antioxidants to prevent or alleviate oxidative stress. Antioxidants scavenge radicals when reduced but their oxidized form may increase oxidative stress and ferroptosis, which emphasizes the importance of monitoring redox reactions dynamically.

Metal chelators

Metal ions such as iron and copper participate in Fenton or Haber–Weiss reactions, producing highly reactive hydroxyl radicals. Metal-binding proteins, such as transferrin and ferritin, sequester free iron to prevent these damaging reactions[18,19]. Intracellular metal homeostasis is tightly regulated by specialized proteins, including metal chaperones that deliver metals to their target proteins[102]. Metallothioneins also help control metal ion availability, reducing their contribution to oxidative damage and ferroptosis[103]. In addition, metal chelator drugs such as deferoxamine, deferiprone, deferasirox and ciclopirox, used in clinical settings, have shown promise in regulating ferroptosis by countering lipid peroxidation processes.

Transcriptional regulators

NFE2L2. In response to oxidative stress or exposure to electrophilic compounds, NFE2L2 is released from Kelch-like ECH associated protein 1 (KEAP1) and translocates into the nucleus. Sequestosome 1 (SQSTM1)-mediated protein degradation regulates the levels of KEAP1, and impaired autophagy leads to SQSTM1 accumulation, resulting in KEAP1 degradation and increased NFE2L2 protein stability[104]. In the nucleus NFE2L2 binds to specific DNA sequences known as antioxidant response elements or electrophile response elements in the promoter regions of target genes. This binding activates the transcription of a set of genes involved in both GPX4-dependent and GPX4-independent pathways to inhibit ferroptosis[105,106]. A key unanswered question is how NFE2L2 selectively activates target genes to inhibit ferroptosis rather than other types of cell death.

TP53. TP53 has a dual role in regulating ferroptosis susceptibility. For instance, the acetylation-deficient TP53 variant TP53(3KR) lacks the ability to induce apoptosis and cell-cycle arrest. However, it retains its capacity for tumour suppression similar to wild-type TP53 by suppressing SLC7A11 expression, thereby increasing ferroptosis sensitivity in certain cancer cells[107]. TP53-mediated downregulation of vitamin K epoxide reductase complex subunit 1 like 1 (VKORC1L1) also increases the ferroptosis sensitivity of cancer cells through vitamin K metabolism[108]. In addition, TP53 positively regulates ferroptosis by inducing the expression of spermidine/spermine N1-acetyltransferase 1 (SAT1), a rate-limiting enzyme in polyamine catabolism that can produce ROS[109]. Conversely, TP53 inhibits ferroptosis under certain conditions. For instance, *TP53* deletion in human colorectal cancer cells increases sensitivity to erastin-triggered ferroptosis through the activation of the DPP4–NOX1 pathway on the cell membrane[30]. Cyclin-dependent kinase inhibitor 1A (CDKN1A; also known as p21), encoded by a classic TP53-inducible gene, also inhibits ferroptosis in cancer cells[110]. Furthermore, the *TP53* mutation R175H yields a modified TP53 protein that functions as a suppressor of ferroptosis by preventing BTB domain and CNC homolog 1 (BACH1)-mediated downregulation of *SLC7A11*, thus promoting tumour growth[111]. These findings underscore the wide implications of TP53 in the modulation of ferroptosis.

ATF4. Activating transcription factor 4 (ATF4) plays a crucial role in endoplasmic reticulum stress and amino acid metabolism. ATF4 activation by endoplasm reticulum stress upregulates anti-ferroptotic genes such as *HSPA5* (ref. 66) and *SLC7A11* (ref. 112). This pathway protects against ferroptosis in cancer cells and mitochondrial cardiomyopathy[113,114]. Sublethal cytochrome *c* release induced by pro-apoptotic BH3 mimetics (ABT-737 and S63845) can lead to ATF4-dependent chemotherapy resistance in cancer cells[115]. Considering the importance of the endoplasmic reticulum as a critical organelle for ferroptosis[61], ATF4 probably plays a specific role in transcriptional regulation, preserving cellular viability and conferring ferroptosis resistance.

Other important transcription factors—including hypoxia-inducible factor 1 subunit α (HIF1A)[116], NF-κB[117], Yes1-associated transcriptional regulator (YAP1)[118,119], WW domain-containing transcription regulator 1 (WWTR; also known as TAZ)[118,119] and sterol regulatory element binding transcription factor 1 (SREBF1; also known as SREBP1)[120]—also play context-dependent roles in shaping the ferroptotic response through multiple targeted genes.

Membrane-repair system

Ca^{2+} is the key initiator of the membrane-repair response. When the plasma membrane is damaged, Ca^{2+} enters the cytoplasm from outside and induces downstream repair processes, such as endosomal sorting complexes required for transport (ESCRT)-III[59,60] and exocytosis[121], thereby enhancing ferroptosis resistance. Efficient membrane repair is vital for cell function and its disruption may be irreversible. However, Ca^{2+} signalling from different organelles has a dual role in the control of ferroptosis sensitivity, underscoring the importance of timely monitoring.

Therapeutic opportunities and challenges

Therapeutic opportunities

Preclinical studies suggest that targeting ferroptosis has broad implications for various diseases, notably in cancer, neurodegenerative disorders and I/R injury, as elaborated below.

Cancer cells often undergo metabolic changes that disrupt redox balance and increase their reliance on antioxidants, making them vulnerable to ferroptosis induction. Targeting ferroptosis offers a potentially effective approach to overcome treatment limitations[107,122–126], despite occasional resistance mechanisms (for example, due to enhanced biosynthesis of pyrimidines[29] or hydropersulfides[127]). Furthermore, specific mutations in genes such as *KRAS* and *TP53* in certain solid cancers are associated with sensitivity to ferroptosis, offering potential precision medicine strategies[1,107,111].

Neurodegenerative disorders, such as Alzheimer's, Parkinson's and Huntington's diseases, involve neuronal destruction and protein aggregation in the brain. Oxidative stress plays a key role in this degeneration, leading to lipid peroxidation and ferroptotic cell death. Therapies that target ferroptosis inhibition aim to reduce oxidative damage and enhance neuron survival[63,128]. Modulation of ferroptosis pathways may help mitigate the accumulation of harmful byproducts such as lipid peroxides and reactive aldehydes, potentially slowing neurodegeneration, including in conditions such as multiple sclerosis[129].

I/R events trigger oxidative stress and cell death, making ferroptosis-targeting therapies promising for mitigating oxidative damage and preserving tissue function in conditions such as stroke and myocardial infarction, as well as kidney and liver injuries. The combination of inhibiting both ferroptosis and necroptosis has been shown to be particularly effective[130,131]. For kidney tubules, ferroptotic cell-death propagation follows a unique pattern that has been referred to as a 'wave-of-death' and has since also been described in other systems[57]. These studies highlight the therapeutic potential of ferroptosis inhibitors in I/R-related diseases.

Therapeutic challenges

Specificity and selectivity. High specificity and selectivity are needed to minimize off-target effects and potential toxicity. For instance, there are concerns about off-target effects of RSL3 and ML162 on the TXNRD1 protein[132]. Imidazole ketone erastin is a widely used in vivo ferroptosis inducer[133] but its activity relative to other in vitro activators needs further study. In addition, inhibition of ferroptosis through antioxidant mechanisms may impact non-ferroptotic pathways, including apoptosis and necroptosis[130,134].

Drug delivery. The development of targeted drug delivery systems is essential to enhance therapeutic effectiveness and reduce systemic side effects. Recent research has shown promise in using nanoparticles—including liposomes, micelles and polymer-based carriers—to address these challenges. Nanoparticles provide advantages such as enhanced drug stability, solubility and targeted delivery.

Biomarker identification. Several biomarkers, such as transferrin receptor[135], ACSL4 (ref. 35), prostaglandin-endoperoxide synthase 2 (ref. 62) and hyperoxidized PRDX3 (ref. 136), have been measured at the messenger RNA or protein levels to monitor ferroptosis responses. Theoretically, blood-based biomarkers have strong translational potential for clinical use, particularly danger signals such as high-mobility group box 1 (HMGB1)[137], ATP[138], SQSTM1 (ref. 139) and decorin[140], which can indicate plasma membrane rupture during ferroptosis. Decorin is notable for its ability to distinguish ferroptosis from other cell-death types, especially in the early stages[140]. Liquid chromatography–mass spectrometry-based redox lipidomics is a

valuable tool for characterizing ferroptotic biomarkers in vivo, especially in various disease conditions[3].

Side effects. The ferroptosis activators that are widely used at present lack cell or tissue selectivity, potentially causing unintended cell death in various immune cell types such as neutrophils[141], $CD8^+$ T cells[142,143], natural killer cells[144] and dendritic cells[145]. Strategies are needed to selectively target tumour cells while preserving immune-cell integrity and anticancer immune responses. A compound called N6F11 has shown promise in selectively inducing ferroptosis in cancer cells, not immune cells, by triggering tripartite motif containing 25 (TRIM25)-dependent GPX4 degradation[69]. Ferroptosis therapy can also lead to adverse effects such as early-onset cachexia[146], stem cell death[147], bone marrow injury[148], haematopoiesis disruption[147] and inflammation-driven tumorigenesis[74,75,114].

Clinical translation. Although some FDA-approved drugs such as sorafenib[78], sulfasalazine[78], artesunate[149] and zalcitabine[51] have shown potential in preclinical ferroptosis induction, their effects may be linked to adverse off-target effects. The identification of safe drugs for patients is crucial, as is considering co-administration of medications to mitigate systemic toxicity and exploring intermittent treatment regimens for better tolerability. Future research should address these aspects to understand ferroptosis in human diseases. Well-designed clinical trials are essential to evaluate the effectiveness, safety and long-term outcomes of ferroptosis-targeting agents. These trials should enrol specific patient populations, identify sensitive ferroptosis biomarkers and measure them alongside clinical outcomes.

Conclusion and outlook

In recent years the field of ferroptosis research has witnessed a remarkable surge, which has become the focus of recent active research[150]. However, the initial definition of ferroptosis as Fe(II)-dependent regulated necrosis accompanied by lipid peroxidation is now recognized as incomplete. Although iron-induced oxidative stress remains a prominent trigger, other iron-independent stimuli or stresses are undoubtedly involved in ferroptosis. Considering that the core downstream feature of ferroptosis is structural damage to cellular membranes resulting from uncontrolled lipid peroxidation, the term 'lipotoxicity' may also reflect its core mechanism.

Molecular mechanisms of ferroptosis have expanded beyond the original GPX4 regulatory pathway. This Review has explored the interplay between pro-ferroptotic mechanisms and anti-ferroptotic mechanisms—categorized as GPX4 dependent and GPX4 independent, respectively—encompassing historical insights and recent findings. However, questions about when, where and how these pathways activate persist.

Numerous regulatory molecules linked to ferroptosis also play roles in other types of cell death, emphasising the complexity of intercellular crosstalk. Untangling these mechanisms requires well-designed experiments, stringent controls and the validation of specific biomarkers. Understanding how physiological and pathological stressors influence ferroptosis in real-world situations remains a challenge. In addition, the intricate connections between stress pathways leading to ferroptotic and non-ferroptotic cell death require further elucidation.

Despite occasional research limitations and conflicting hypotheses, we maintain optimism about the future prospects of ferroptosis. We believe that the principles of ferroptosis will eventually find clinical applications beyond their heuristic value.

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Acknowledgements

The authors thank all of the pioneers in the field and our colleagues who contributed to the study of the process and function of ferroptosis. The lead contact D.T. is supported by grants from the US National Institutes of Health (R01CA160417, R01CA229275 and R01GM127791).

Competing interests

B.R.S. is an inventor on patents and patent applications involving ferroptosis, co-founded (and serves as a consultant to, ProJenX and Exarta Therapeutics, holds equity in Sonata Therapeutics and serves as a consultant to Weatherwax Biotechnologies Corporation and Akin Gump Strauss Hauer & Feld LLP. B.G. is an inventor on patent applications involving targeting ferroptosis in cancer therapy and reports personal fees from Guidepoint Global, Cambridge Solutions and NGM Bio. D.I.G. is an employee and shareholder of AstraZeneca. V.G.S. serves as an advisor to, and/or has equity, in Branch Biosciences, Ensoma and Cellarity (all unrelated to the present work). L.G. has/had research contracts with Lytix Biopharma, Promontory and Onxeo; received consulting/advisory honoraria from Boehringer Ingelheim, AstraZeneca, OmniSEQ, Onxeo, The Longevity Labs, Inzen, Imvax, Sotio, Promontory, Noxopharm, EduCom and the Luke Heller TECPR2 Foundation; and holds Promontory stock options. A.I.B. holds shares in Cogstate Ltd, Alterity Ltd and a profit share with Collaborative Medicinal Development LLC, and acts as a paid consultant to Collaborative Medicinal Development LLC. X.J. is an inventor of patents related to autophagy and cell death, and holds equity in, and also consults for, Exarta Therapeutics and Lime Therapeutics. G.K. has research contracts with Daiichi Sankyo, Eleor, Kaleido, Lytix Pharma, PharmaMar, Osasuna Therapeutics, Samsara Therapeutics, Sanofi, Tollys, and Vascage; is on the Board of Directors of the Bristol Myers Squibb Foundation France; is a scientific cofounder of everImmune, Osasuna Therapeutics, Samsara Therapeutics and Therafast Bio; is on the scientific advisory boards of Hevolution, Institut Servier and Longevity Vision Funds; and is the inventor of patents covering therapeutic targeting of ageing, cancer, cystic fibrosis and metabolic disorders. G.K.'s wife, L. Zitvogel, has held research contracts with GlaxoSmithKline, Incyte, Lytix, Kaleido, Innovate Pharma, Daiichi Sankyo, Pilege, Merus, Transgene, 9 m, Tusk and Roche; she was on the Board of Directors of Transgene, is a cofounder of everImmune and holds patents covering the treatment of cancer and the therapeutic manipulation of the microbiota. G.K.'s brother, R. Kroemer, was an employee of Sanofi and now consults for Boehringer Ingelheim. The remaining authors declare no competing interests. The funders had no role in the writing of the manuscript.

Additional information

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Peer review information *Nature Cell Biology* thanks Graeme Lancaster, Maureen Murphy and Tobias Dansen for their contribution to the peer review of this work.

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